REMARKS

Claims 1-4, 6-7, 10, and 16-28 were pending in the present application. Claims 1 and 24 have been amended herein, support for which can be found throughout the specification. No new matter has been added. Upon entry of the present amendment, claims 1-4, 6-7, 10, and 16-28 will remain pending.

As a preliminary matter, claim 24 has been amended, as suggested by the Examiner, to correct a typographical error.

I. The Claimed Invention Is Not Obvious

Claims 1-4, 6 and 7 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the combination of U.S. Patent No. 5,620,989 (hereinafter, the "Harrison reference") and PCT Publication No. WO 00/02859 (hereinafter, the "Bernstein reference"). Applicants traverse the rejection and respectfully request reconsideration thereof.

The Office asserts that the claimed compounds differ from the Harrison reference "only in the substitution of a naphthyl amide group for phenoxy" (see, Office Action at page 5). As an aside, the phenoxy group referred to by the Office is actually a benzyloxy group. The Office then mistakenly concludes that it would have been *prima facie* obvious for one skilled in the art to "use analogs of those of Harrison et. al. to produce the instant invention" (see, Office Action at page 7).

What the Office appears to have done, however, is examine the structure of Applicants' claimed compounds and then piece together two structures from two different sets of compounds reported in two references to deprecate Applicants' claimed invention. Applicants note that "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). Under this standard, none of the prior art of record, alone or in any proper combination, discloses or suggests Applicants' claimed invention.

In this regard, one skilled in the art having examined both the Harrison reference and the Bernstein reference would have no motivation to delete roughly half of the structure of the Harrison compounds and replace it with half the structure of the Bernstein compounds. Indeed,

the only "motivation" identified by the Office is that one skilled in the art "would be motivated to prepare these compounds on the expectation that **such close analogues** would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry" (emphasis added; see, Office Action at page 7). One skilled in the art, however, would NOT consider the compounds of the Harrison reference to be "close analogues" of the compounds of the Bernstein reference. Indeed, they are quite different compounds. For example, as stated above, the compounds of the Harrison reference have a benzyloxy group compared to the naphthyl amide group of the Bernstein reference. This departure alone is sufficient to counter the Office's "close analog" premise. Further, a carbon of the phenyl group is directly bonded to a carbon within the piperidinyl group of the Harrison compounds, whereas in the Bernstein reference, there is a propylene group between the nitrogen of the piperidinyl group and a carbon of the phenyl group. Thus, the compounds of the Harrison and Bernstein references are NOT "close analogues."

Further, there is no teaching or suggestion in either of the two references for making the specific combination asserted by the Office. Indeed, one skilled in the art could retain the benzyloxy group of the Harrison reference and replace the remainder of the compound with the corresponding portion of the compounds reported in the Bernstein reference. Further, one skilled in the art could replace less than half of the Harrison compounds with less than half of the Bernstein compounds. For example, one skilled in the art could choose to replace only the benzyl portion of the benzyloxy group of the Harrison reference with the naphthyl amide group of the Bernstein reference. Indeed, there are numerous ways to combine portions of the Harrison compounds with portions of the Bernstein compounds – but it is only upon examining Applicants' specification that one particular combination becomes apparent. Thus, the combination of references is improper for its use of hindsight reconstruction based upon Applicants' disclosure. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.").

Thus, the claimed invention is not obvious in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

II. Obviousness-Type Double Patenting

Claims 1-4, 6, 7, 10, and 16-28 are provisionally rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-13 of co-pending application Serial No. 10/539,140 (hereinafter, the "'140 application") in view of Elliot et. al., Bioorganic & Med. Chem. Lett., 2002, 12, 1755-1758 (hereinafter, the "Elliot reference"). Applicants traverse the rejection and respectfully request reconsideration thereof.

The Office asserts that the "instant claims differ from those of the '140 application by the identity of the moiety linking the naphthyl ring to the piperidine. This change is taught by Elliot et. al. in his NK-1 antagonists" (see, Office Action at page 18). Thus, the Office appears to suggest that it would be obvious to modify the compounds recited in claims 1-13 of the '140 application by replacing the $-CH_2-N(-R^7)-CH_2-$ "linker" with the $-CH_2-N(-R^2)-C(=O)-$ "linker" recited in the claims of the present application.

The Office is reminded that the $-CH_2-NH-C(=O)-$ "linker" reported in the Elliot reference actually links a di-(trifluoromethyl)phenyl group to a cyclohexyl group (which is further substituted by a phenyl group and a piperidine group (which itself is further substituted with a fluorinated phenyl group). Thus, the Elliot compounds comprising the "linker" are quite different than Applicants' claimed compounds or the compounds of the '140 application. There is no suggestion or teaching in the Elliot reference, or in any reasoning provided by the Office, that would motivate one skilled in the art to modify any molecule, despite how structurally dissimilar, to contain such a linker. It is only upon examining Applicants' specification that one particular "linker" becomes apparent. Thus, the combination of references is improper for its use of hindsight reconstruction based upon Applicants' disclosure. *In re Fine*, *Id.*

In addition, claims 1-4, 6, 7, 10, and 16-28 are provisionally rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-12 of co-pending application Serial No. 10/527,280 (hereinafter, the "'280 application") in view of the

Elliot reference. Applicants traverse the rejection and respectfully request reconsideration thereof.

The Office asserts that the "instant claims differ from those of the '280 application by the identity of the moiety linking the naphthyl ring to the piperidine. This change is taught by Elliot et. al. in his NK-1 antagonists" (see, Office Action at page 20). Thus, the Office appears to suggest that it would be obvious to modify the compounds recited in claims 1-12 of the '280 application by replacing the -C(R^4R^5)-O-C(R^6R^7)- "linker" with the -CH_2-N(-R^2)-C(=O)- "linker" recited in the claims of the present application.

The Office is again reminded that the -CH_2-NH-C(=O)- "linker" reported in the Elliot reference actually links a di-(trifluoromethyl)phenyl group to a cyclohexyl group (which is further substituted by a phenyl group and a piperidine group (which itself is further substituted with a fluorinated phenyl group). Thus, the Elliot compounds comprising the "linker" are quite different than Applicants' claimed compounds or the compounds of the '280 application. There is no suggestion or teaching in the Elliot reference, or in any reasoning provided by the Office, that would motivate one skilled in the art to modify any molecule, despite how structurally dissimilar, to contain such a linker. It is again only upon examining Applicants' specification that one particular "linker" becomes apparent. Thus, the combination of references is improper for its use of hindsight reconstruction based upon Applicants' disclosure. *In re Fine*, *Id*.

III. The Claimed Invention Is Supported by Ample Written Description

Claim 1 is rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter. The Office asserts that deletion of the phrase "where at least one R^1 moiety is other than hydrogen" creates "a genus of compounds not described in the specification" (see, Office Action at page 4). Although Applicants disagree, solely to advance prosecution of the present application, claim 1 has been amended herein to further recite "where at least one R^1 moiety is other than hydrogen." In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, as allegedly presenting new matter be withdrawn.

IV. The Claimed Invention Is Enabled

A. Claims 1 and 6

Claims 1 and 6 are rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to meet the enablement requirement. Applicants traverse the rejection and respectfully request reconsideration thereof in view of amended claim 1.

The Office asserts that:

> the naphthyl moiety R1 substituents contain numerous inoperative embodiments in particular the olefins and alkynes and the Ra and Rb taken together to form a ring. If these embodiments were removed the scope of the claim would be acceptable.

(see, page 2 of the Office Action). Although Applicants disagree with the reasoning for the rejection, solely to advance prosecution of the present application, Applicants have amended claim 1 to delete "$C_{2\text{-}4}$alkenyl, $C_{2\text{-}4}$alkynyl," and "or, R^a and R^b together are $(CH_2)_jG(CH_2)_k$." Thus, the scope of the claims now corresponds to the scope of the claim indicated by the Examiner as being acceptable. In light of the foregoing discussion, Applicants respectfully assert that claims 1 and 6 meet the requirements of 35 U.S.C. §112, first paragraph, and request the claim rejection be withdrawn.

B. Claims 10 and 16-28

Claims 10 and 16-28 are rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to meet the enablement requirement regarding use of the claimed invention. Applicants traverse the rejection and respectfully request reconsideration thereof.

As a preliminary matter, claims 24 and 25 do not recite methods. Accordingly, Applicants submit that these two claims were erroneously included within the present enablement rejection.

As will be recognized, the enablement requirement of § 112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under §112 is whether one skilled in the

art would be able to practice the invention without undue experimentation). In this respect, the following statement from *In re Marzocchi*, is noteworthy:

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling.
>
> … it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971) (emphasis added). Thus, any assertion by the Patent Office that an enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974).

The Office has not carried its burden under *In re Marzocchi*. Further, the claimed methods can be used without undue experimentation. As asserted in Applicants' specification, the compounds have both NK_1 antagonist and serotonin reuptake inhibitory (SRI) activity. There is ample evidence of the efficacy of NK_1 antagonists and SRI's for treating depression and anxiety. For example, McLean, Curr. Pharm. Design, 2005, 11, 1529 (hereinafter, the "McLean reference") summarizes the results of 19 positive preclinical studies showing the anxiolytic effect of NK_1 antagonists and 14 positive studies showing the antidepressant effect of NK_1 antagonists, all published prior to the filing date of this application (see, Table 2, pages 1536-37 of the McLean reference). The anxiolytic and antidepressant effect of NK_1 antagonists is further supported by the articles cited within Applicants' specification, showing the involvement of NK_1

receptors in depression and a decrease in the anxiety behavior of mice following administration of NK_1 antagonists (Papp et al., Behav. Brain Res., 2000, 115, 19; and Santarelli et al., Proc. Nat. Acad. Sci., 2001, 98, 1912; cited in the specification at page 1, line 30, through page 2, line 2). Moreover, serotonin reuptake inhibitors were well-known to have efficacy in treating anxiety and depression (Boerner and Moeller, Pharmacopsychiatry, 1999, 32, 119-26). Hence, there is a clear link between the treatment of depression and anxiety and NK_1 antagonist and serotonin reuptake inhibition activity. Accordingly, one of skill in the art would be able to practice the claimed methods of treating depression and generalized anxiety disorder without undue experimentation.

The Office counters Applicants' evidence (i.e., Applicants' specification and the citation of four references) by pointing out that Gerspacher, Prog. Med. Chem., 2005, 43, 49-103 (hereinafter, the "Gerspacher reference") "illustrates the very real lack of unpredictability even with clinical data" (see, Office Action at page 3). As a preliminary matter, the compound reported in the Gerspacher reference (i.e., Aprepitant) is structurally quite different than the compounds recited in Applicants' claims. The portion of the Gerspacher reference actually referred to by the Office, however, does not support the Office's position. Indeed, the Gerspacher reference reports:

> Antidepressant efficacy of the NK1 antagonist Aprepitant (MK869) (6) could be demonstrated in a placebo controlled clinical study where a dose of 300 mg (p.o. once daily) of Aprepitant was administered to patients suffering from major depressive disorder for 6 weeks. In this study, Aprepitant was well tolerated and the effectiveness of the compound as an antidepressant agent was comparable with that of the serotonin uptake inhibitor paroxetine [22, 23].

Thus, this portion of the Gerspacher reference does not support the Office's position.

The Gerspacher reference further reports "In later studies, however, the antidepressant activity of Aprepitant could not be confirmed [24]." The Gerspacher reference does not report that the previous studies were flawed, just that they could not be confirmed. This does not amount to being required to perform undue experimentation. Indeed, the "later studies" may not have had similar results dues to any number of reasons, none of which are explained in the Gerspacher reference to any degree. Thus, one skilled in the art is left to wonder why the "later

studies" did not confirm the earlier studies.

The Gerspacher reference further reports "the existing experimental evidence suggest that substance P and the NK1 receptor are important players in the pathophysiology of central nervous diseases such as depression [18]…" This statement also does not support the Office's position. The The Gerspacher reference further reports "the **partially** negative results with Aprepitant are contradictory to this and additional studies will be needed to get conclusive answers on the antidepressant potential of neurokinin antagonists" (emphasis added). The fact that experimental results are "partially" negative does not mean that undue experimentation is required to practice the claimed invention. Again, no reason is provided in the Gerspacher reference indicating why the results were "partially negative." Further, Applicants respectfully assert that clinical trials may fail (or partially fail, as it appears in the present case) for a variety of reasons, including safety concerns which are outside the purview of the U.S. Patent and Trademark Office. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994).

The only other evidence proffered by the Office is Kenakin et al., TRENDS in Pharmacol. Sciences, 2002, 23, 275-280 (hereinafter, the "Kenakin reference"). The Office asserts that the Kenakin reference reports that:

> all ligands with macro-affinity should be extensively studied for pharmacological activities other than simple G-protein activation because various physiological activities have been defined that are mediated by conformations not necessarily related only to G-protein activation…Ligand activities that are not related to a standard G-protein-mediated physiological response **might have therapeutic utility**.

(See, Office Action at page 17). As a preliminary matter, the Office has pieced together sentences from 4 different paragraphs (Applicants reproduced above only a portion of the entire quotation from the Office Action in which sentences from 3 different paragraphs were pieced together). When the Kenakin reference reports that all ligands with macro-affinity should be extensively studied, the Kenakin reference further states (in the same section) that:

> These types of data emphasize the idea that the non-observance of efficacy does not necessarily imply the absence of efficacy, that is the appropriate assay is needed to detect conformational change.

Thus, the Kenakin reference merely teaches that additional assays should be used when efficacy

is not observed. This report, however, does not support the notion that undue experimentation is required to practice the claimed invention.

Applicants fail to understand how the statements identified in the Office Action regarding the Kenakin reference support the Office's position. Rather, Applicants submit that this portion of the Kenakin reference reports that the skilled artisan should perform more than G-protein activation assays because other physiological activities have been identified that are not necessarily related only to G-protein activation. Indeed, these other ligand activities that are not related to a standard G-protein-mediated physiological response might also have therapeutic utility.

The evidence provided by Applicants supporting their position that no undue experimentation is required to practice the claimed methods (i.e., Applicants' specification and several references) overwhelms the two citations referred to by the Office. Thus, the weight of the evidence tips in Applicants' favor. In light of the foregoing discussion, Applicants respectfully assert that methods of claims 10 and 16-28 meet the requirements of 35 U.S.C. §112, first paragraph, and request the claim rejection be withdrawn.

IV. Conclusion

Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (610) 640-7854 to resolve any remaining issues.

The Commissioner is hereby authorized to debit any underpayment of fee due or credit any overpayment to Deposit Account No. 50-0436.

Respectfully submitted,

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